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August 2, 2000

<u>MEMORANDUM</u>

SUBJECT: ***LINDANE* -** Report of the FQPA Safety Factor Committee

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Sue Shallal, Risk Assessor
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PC Code: 009001

The FQPA Safety Factor Committee met on July 24, 2000 to evaluate the hazard and exposure data bases for lindane and concluded that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) for use in human health risk assessment be reduced to 3x.

I. HAZARD ASSESSMENT

(*Memorandum:* S. Shallal to M.T. Howard dated July 27, 2000)

A. Adequacy of the Toxicology Database

There are two developmental studies conducted in rats and rabbits in which Lindane is administered via the oral and subcutaneous (4 studies in all). Although the rabbit studies were classified as unacceptable, the HIARC concluded that a new developmental toxicity study in rabbits is not required (see Section I.B. below or refer to the HIARC document for details). An acceptable 2-generation reproductive study is also available, as well as, acute, subchronic and developmental neurotoxicity studies.

B. Determination of Susceptibility

The data provided no indication of quantitative or qualitative increased susceptibility/sensitivity in rats following *in utero* exposure to lindane. In the prenatal developmental toxicity studies in rats, developmental effects were observed only at or above doses causing maternal toxicity.

The prenatal developmental study in rabbits is classified as Unacceptable (not upgradable) since maternal and developmental toxicity LOAELs were not identified and the highest dose did not approach the limit dose. Therefore, dose selection was considered inadequate. Doses were based on the results of a subcutaneous study in the rabbit (MRID 00062658) which is not a valid method for selecting doses for an oral study. Several other deficiencies were noted in the conduct of this study: percent purity of the test article was not given, dosing solutions were not analyzed for concentration, stability, or homogeneity, and much of the individual animal data were not included.

Although the developmental toxicity study in rabbits was classified unacceptable, the HIARC concluded that a new study is not required because: 1) The developmental toxicity study in rabbits and rats using a subcutaneous route of administration shows no developmental effects at the maternally toxic dose; 2) The skeletal effects observed in the developmental toxicity study in rats, with gavage as the route of administration, are within historical controls; 3) More severe maternal effects are seen in the rabbit study with subcutaneous administration; 4) The rat appears to be the more sensitive species for developmental effects; 5) A developmental neurotoxicity study has already been submitted.

There was, however, evidence of qualitative increased susceptibility in the rat multi-generation reproduction study:

> Both parental and offspring LOAELS are 13 mg/kg; however there is a qualitative difference in effects. In the parental animals, toxicity was seen in the form of reduction in body weight gain during gestation while offspring toxicity was correlated with decreases in pup viability and pup body weight in the F_1 and F_2 generations as well as

> delayed maturation in the F_2 generation. Evidence for quantitative increase in susceptibility could not be ascertained due to the wide spread in the doses tested.

There is also quantitative increased susceptibility demonstrated in the rat developmental neurotoxicity study:

> Maternal toxicity observed at 120 ppm (13.7 mg/kg/day, LOAEL) is based on decreased body weight gains, decreased food consumption, and increased reactivity to handling (maternal NOAEL is 50 ppm; 5.6 mg/kg/day). Offspring toxicity was observed at 50 ppm (5.6 mg/kg/day, LOAEL) and is based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation (NOAEL is 10 ppm; 1.2 mg/kg/day).

The offspring effects seen in the developmental neurotoxicity study were the same as those seen in the the two-generation reproduction study - no additional functional or morphological hazards to the nervous system were noted.

C. Studies from the Literature

The open literature does contain citations which suggest an increase in susceptibility of fetuses and young animals exposed to lindane. The transfer of lindane via mother's milk also seems to be efficient, as well as, its metabolism into pentachlorobenzene (refer to the HIARC document for details).

II. EXPOSURE ASSESSMENTS

A. Dietary (Food) Exposure Considerations

(*Correspondence:* T. Morton to B. Tarplee dated July 15, 2000)

The registrant is supporting the use of lindane on barley, broccoli, brussels sprouts, cabbage, cauliflower, corn, lettuce, oats, radish, rye, sorghum, spinach, and wheat. Only seed treatment uses remain on the label. Seed treatment application rates range from 0.33 to 3.57 oz. a.i./cwt of seed. For comparison, the 3.57 oz. a.i./cwt application rate is equivalent to 0.04 lb. a.i./acre. Since the only supported use is seed treatment, application is made only once per season.

Tolerances are currently established for residues of the insecticide lindane (gamma isomer of benzene hexachloride) in or on many raw agricultural commodities at levels ranging from 0.01ppm (pecans) to 7ppm (meat fat). Codex MRLs range from 0.01 ppm in milk to 3 ppm in cranberry and strawberry. Codex MRLs for supported crops in the US are 0.5 ppm for brussels sprouts, cabbage, cauliflower, and cereal grains; 0.1 ppm for eggs; 2 ppm for head lettuce, meat of cattle, pigs, and sheep, and spinach; and 1 ppm for radish.

The MARC has determined that until adequate seed treatment metabolism studies are submitted, the total radioactive residues will be used for risk assessment purposes. In a confined rotational crop study, radioactive lindane was found in barley forage but not barley grain. It was also found in carrot tops and to a lesser extent in mature lettuce.

No monitoring data is available which would definitively include lindane only from seed treatment uses. However, it may be possible to use available monitoring data for foliar uses on imported commodities. Field trials were conducted on wheat, feeding studies on ruminant and poultry, but will not be used since the MARC has concluded that the total radioactive residues must be used for risk assessment purposes.

In 1998, BEAD provided percent crop treated data for small grains (7 % crop treated), field corn (6 % crop treated), and sorghum (10 % crop treated). HED has asked BEAD to supply current % crop treated data for the above crops and any other of the supported crops.

The Dietary Exposure Evaluation Model (DEEM) is used to estimate the dietary risk resulting from the residues of lindane on foods. The DEEM analyses are refined using the available %CT data.

B. Dietary (Drinking Water) Exposure Considerations
(*Correspondence:* D. Young to B. Tarplee, dated July 10, 2000.)

The environmental fate database for lindane is adequate to characterize the potential for contamination of drinking water sources. These data indicate that parent lindane is persistent and moderately mobile. It is transported through the environment by both hydrologic and atmospheric means. It is resistant to photolysis and hydrolysis (except at high pH), and degrades very slowly by microbial actions (980 day soil half life).

Degradates are predominantly benzene hexachloride, pentachlorocyclohexane, 1,2,4,-trichlorobenzene, and 1,2,3-trichlorobenzene. In submitted studies, degradates were observed at much less than 10% of applied.

Currently, U.S. agricultural uses of lindane are restricted to seed treatments, and application rates are quite low. Even under these restriction, however, lindane may reach water resources at levels above the Maximum Concentration Level (MCL = 0.2 µg/L).
Monitoring data are available which demonstrate the presence of lindane in the environment:

> In the U.S. EPA STORET data base, 720 detections (after culling of data to eliminate dubious data, e.g. K and U codes) in ground water were reported between the years 1968 and 1995, in nearly all regions of the country, with especially high numbers of detections in the South and West. For these 720 detections, the median and mean concentrations were 0.01 and 11 µg/L, respectively. For surface waters, 8775 detections were reported with median and mean concentrations of 0.005 and 0.18 µg/L. STORET Detections were reported in nearly all regions of the conterminous U.S.

In the USGS NAWQA study, lindane was detected in 2.58% of surface water samples (0.67% at levels greater than 0.05 mg/L, maximum concentration reported was 0.13 mg/L). For groundwater, USGS NAWQA reported a detection frequency of 0.1 % (0.07% at levels greater than 0.01 mg/L, maximum concentration reported was 0.032 mg/L).

Since all monitoring data represent detections resulting from all previous uses of lindane (including foliar uses which are currently not supported by the registrant), models were used to calculate the estimated environmental concentrations (EECs): GENEEC model for surface water; and SCI-GROW for ground water.

Due to the persistence of lindane, its past wide-spread use, and its mobility by both atmospheric at hydrologic means, the extent of population exposed could be high in comparison to other chemicals.

C. Residential Exposure Considerations

(*Telephone communication:* D. Jaquith on July 19, 2000)

Only seed treatment uses remain on the label for lindane. There are no registered residential uses and therefore, residential exposure to lindane is not expected.

III. SAFETY FACTOR RECOMMENDATION, RATIONALE, AND APPLICATION

A. Recommendation of the Factor

The Committee recommended that the FQPA safety factor for protection of infants and children (as required by FQPA) should be **reduced to 3x** for lindane.

B. Rationale for the Selection of the FQPA Safety Factor

The FQPA SFC concluded that a safety factor is required for lindane since there is evidence of increased susceptibility of the young demonstrated in both the developmental neurotoxicity study (quantitative) and the 2-generation reproduction study in rats (qualitative).

The Committee recommended that the **FQPA safety factor** be **reduced** to 3x because: 1) the toxicology data base is complete; 2) the available data provide no indication of quantitative or qualitative increased susceptibility in rats from *in utero* exposure to lindane in the prenatal developmental study; 3) although the developmental toxicity study in rabbits was classified unacceptable, the HIARC concluded that a new study is not required (See Section I.B.); 4) the offspring effects seen in the developmental neurotoxicity study were the same as those seen in the the two-generation reproduction study (no additional functional or morphological hazards to the nervous system were noted); and 5) adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess food exposure and to provide a screening level drinking water exposure assessment; and 6) there are currently no residential uses.

C. Application of the Safety Factor - Population Subgroups/Risk Assessment Scenarios

The FQPA safety factor for lindane is applicable to **All Population Subgroups** for **Acute and Chronic Dietary Risk Assessments** (there are currently no residential scenarios), since there is concern for increased susceptibility of the young demonstrated in the developmental neurotoxicity study and in the 2-generation reproduction study.